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International patent application PCT/EP2005/050812
Octapharma AG

Via facsimile and confirmation copy
21 December 2005

Our Ref:
050036WO Me/do

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Extension - 214

Responsive to the Written Opinion of the International Searching Authority of 6 October 2005:

A new set of claims is submitted. The phrase "at about 4.6 / to about 4.95, in particular" and "about" in feature (b) of former claim 1 has been deleted. This reflects the cited prior art in form of D1 or D2. Neither D1 nor D2 are teaching to maintain the pH at 4.8 to about 4.95 since no measures are shown for keeping the pH at this level. Of course, if caprylic acid is added according to D1 the pH would still be lower. Whereas according to the invention the pH has to be kept stable [feature 1 (b)]. Furthermore, it becomes evident that the present invention does not employ a pH-shift as taught by D3.

Thus, the present invention is not anticipated by D1 or D2.

With regard to inventive step it is pointed out that according to applicant's view not D1 but D3 should be regarded as

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closest prior art. The difference between D3 and the present invention is to a great extent the waving of the pH-shift step which is essential according to D3.

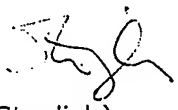
The skilled person did not have any incentive to wave the pH-shift step according to D3 or combine the teaching of D3 with D1, D2 or a combination thereof. By the way, this would also not lead to a waving of the pH-shift, because the references D1 and D2 do not deal with a shift caused by the addition of caprylate but with a shift occurring when adding the free caprylic acid. The skilled person did not have any incentive to amend or change the experimental conditions as taught by the references, in particular D3. At least the Searching Authority does not give any motivation the skilled person would have to do so. It is applicant's believe that an unexpected effect associated with an allegedly "slight" modification is an indication of inventive step. The IPEA's attention is drawn to the table on pages 13/14. From this it becomes evident that the allegedly "slight" modification, which is indeed a significant one, leads to a significant depletion of unwanted protein in the antibody preparation according to the invention. This becomes evident by comparison of column 3 of the table (which is according to the invention) when maintaining the pH as 4.9 with column 4, representing values obtained according to D3. In all experiments done, the albumin content is depleted about the factor of about 10 whereas the IgG-content was kept comparibly. It could not be foreseen that this crucial effect was associated with a change of the pH-conditions, i.e. to keep the pH constant during caprylate addition versus the method disclosed in D3.

By the way, D3 seems to be the closest prior art since in the later disclosure also caprylate is added whereas in D1 and D2 according to the Searching Authority caprylic acid has been used.

It is requested to acknowledge novelty and inventive step of the subject matter of the present set of claims. The deficiencies mentioned under item VIII will be addressed when entering national or regional stages, if necessary.

The document WO 2005/073252 A1 which was addressed in Section VI is of no relevance due to the fact that caprylic acid as precipitated agent is used and not caprylate.

Patent Attorney



(Dr. Steglich)

Enclosure:

- New set of claims 1-23

Claims

1. A method of preparing a purified, virus inactivated and virus safe antibody preparation from a starting solution comprising antibodies and contaminants, the method comprising the steps of:

   (a) adjusting the pH of the starting solution to about 4.6 to about 4.95, in particular to about 4.8 to about 4.95 to produce an intermediate solution;

   (b) adding caprylate and/or heptanoate ions to the intermediate solution and maintaining the pH ~~at about 4.6 to about 4.95, in particular~~ at ~~about~~ 4.8 to about 4.95, whereby a precipitate is formed and the antibodies are essentially present in the supernatant;

   (c) incubating the supernatant solution under conditions of caprylate and/or heptanoate ion concentration, time, pH and temperature optionally concentrating and diafiltrating the filtrated solution before pH adjustment;

   (d) applying the filtered solution with a least one anion exchange resin and optionally with two different anion exchange resins under conditions that allow binding of contaminants to the resin while not allowing significant binding of the antibodies to the resin, wherein a purified, virus inactivated and virus safe antibody preparation is produced.

2. The method of claim 1 wherein in step (d) the virus inactivated solution is contacted with the at least one anion exchange resin at a pH from about 5.0 to 5.2.

3. The method of claim 1 and/or 2 wherein a second anion exchange chromatography is performed at a pH range of from 6.7 to 6.9.

4. The method of claims 1 to 3 wherein steps (b) and (c) are repeated at least one time.

5. The method of claims 1 to 4 wherein the starting solution comprises plasma-derived antibodies.

6. The method of claims 1 to 5 wherein in step (d) the inactivated solution is contacted with two different anion exchange resins under conditions such

that contaminants are selectively bound to the resins while the antibodies, are not significantly bound to the resins.

7. The method of claims 1 to 6, wherein the antibodies are immunoglobulin G.

8. The method of claim 6, where the pH is adjusted to pH 6.8 ± 0.1 prior to the second anion-exchange chromatography.

9. The method of claims 1 to 8, wherein the anion-exchange chromatography flow-through is concentrated to 60 to 90 mg/ml and diafiltrated against a buffer solution, preferably a phosphate buffer.

10. The method of claims 1 to 9, wherein the flow-through of the first anion-exchange chromatography is solvent detergent treated, preferably by Triton X-100 and TnBP, most preferred by concentrations of 1% Triton X-100 and 0.3% TnBP for 4.5 to 8 hours to inactivate lipid coated viruses.

11. The method of claim 10, the detergents of the incubation mixture of which are removed by solid and liquid phase extraction.

12. The method of at least any one of claims 1 to 11 wherein at least one of the methods selected from the group consisting of UV-C treatment, heat-treatment, virus filtration and prion removal or inactivation is combined with a caprylate treatment of claim 1.

13. The method of claim 11, wherein the pH value upon solid phase extraction is adjusted to 6.7 to 6.9.

14. The method of claim 13, wherein the solution is submitted to the second anion-exchange chromatography.

15. The method of claim 14, wherein the pH value of the anion-exchanger flow-through is adjusted to 3.5 to 4.5, preferably to pH 4.0 ± 0.1.

16. The method of claim 15, wherein the IgG solution is contacted by a virus filter.

17. The method of claim 15, wherein the IgG solution is contacted by a nanofilter.

18. The method of claim 15 wherein the IgG solution is incubated for at least 24 hours, preferably at 37°C± 1.

19. The method of claim 15, wherein the IgG solution is concentrated to 5 or 10%.

20. The method of claim 19, wherein the osmolarity of the concentrate is adjusted to 200 to 400 mOsmol/kg by an appropriate additive.

21. The method of claim 20, wherein the IgG solution is pH adjusted to 3.5 to 6.0, preferred to a pH value of 4.0 to 5.5.

22. The method of claim 21 wherein the IgG solution is sterile filtered and filled in glass bottles or plastic containers.

23. An IgG containing fraction obtainable according one of the claims 1 to 22.